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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,448	11/27/2000	Susan J. Clark	Q-61152	5339

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,448	CLARK ET AL	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,19-21,23,26-29,49,50 and 77-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-14,19-21,23,26-29,49,50 and 77-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1105
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed January 23, 2005. Currently, claims 1, 3-14, 19-21, 23, 26-29, 49-50, 77-109 are pending. Claims 49-50 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims or applicant's remarks.

4. This action contains new grounds of rejection necessitated by amendment.

5. This action is FINAL.

Priority

6. This application claims priority to PCT/AU99/00306, filed April 23, 1999 and Australian PP 3129, filed April 23, 1998.

It is noted that the priority document does not appear to contain support for differential methylation in liver cancer tissue DNA extracts. Figure 9 of the instant application appears to be first present in the PCT/AU99/00306. Therefore, Claims directed to liver cancer are not supported by the Australian PP 3129 document and receive the benefit of April 23, 1999.

The examiner has reviewed the priority document with respect to the presence of liver cancer. While there is no intervening art on record and therefore the observation does not appear to affect any of the rejections of record, the teachings in the priority

document do not provide an enabling disclosure that liver cancer contains differential methylation.

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

New Grounds of Rejection Necessitated by Amendment

New Matter

8. Claims 1, 3-14, 19-21, 23, 26-29, 77-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "SEQ ID NO: 60" is included. The amendment to add SEQ ID NO: 60 does not appear to be supported by the original specification. MPEP 608.01 (p) provides "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing

such reference for the purpose of the disclosure required by 35 U.S.C.112, first paragraph.*In re de Seversky* ,474 F.2d 671,177 USPQ 144 (CCPA 1973)." Here, the brief description of figures states that Figure 1 shows the organization and nucleotide sequence of the human GST-Pi gene. The description states that the GST-Pi gene sequence of Genbank Accession No. M24485 (page 12 of specification). Figure 1 depicts particular regions of the gene, however, does not provide the full nucleotide sequence for the gene. It is clear that the full gene sequence is not provided in the instant application. It is also clear that the specification fails to incorporate the sequence by reference, as there is no root words "incorporate(e)" and "reference" within the text. The specification as originally filed does not demonstrate a clear intent to incorporate the sequence by reference. The Genbank Accession number was not presented in any of the claims or specifically incorporated by reference. Therefore SEQ ID NO: 60 constitutes new matter.

Even in the event that SEQ ID NO: 60 did not constitute new matter, the specification does not teach the nucleotide sequence for the "-29", "+11", "+12", "+55" and numerous sites beyond "+55" CpG sites. Figure does not contain any "+55" site. Further it is unclear whether "-14" CpG site is 1117 or 116 of SEQ ID NO: 60, as the claims appear to encompass both nucleotides.

Further, the claims are drawn to a method of a diagnostic or prognostic assay for liver cancer by determining abnormal methylation of cytosine by amplifying sites -43-14 and +9-+55. The specification teaches liver cancer was analyzed and normal liver tissue was shown to be partially methylated in the region of the transcription site -7- +7

(page 30). The specification teaches that the primer pairs encompass sites -39 to -16. The specification fails to provide any support or teachings to -43 to -14 or +9 to +55. The region of +9 to +55 do not appear to be taught as sites for analysis of liver cancer. The specification specifically teaches away from using the region between -7 to +7, therefore, Claim 106 directed to CpG sites -43 to +55 does not appear to be contemplated in the instant specification. The guidance provided in the specification would not have been to develop a method comprising regions which were specifically taught away from in the specification. With respect to the particular sites -36, -32, -23, -20, -19 and -14, the instant specification does not appear to support these particular sites with liver cancer. These sites are not provided for in the ranges taught in the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-14, 17-25 and newly added claims 75-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June 1997) in view of Herman et al. (US Pat. 5,786,146, July 1998).

Lee et al. (herein referred to as Lee) teaches CG island methylation changes near the GSTP1 gene in prostatic carcinoma cells detected using the polymerase chain reaction: a new prostate cancer biomarker. Lee teaches isolating DNA from normal and neoplastic cells and tissue from prostate carcinoma specimens (page 443, col. 2)(limitations of Claim 1 (i), 14-17, 44-47). Lee teaches that the DNA specimens were subjected first to exhaustive digestion with excess HpaII, which cuts the unmethylated sequence (page 443, col. 2). The samples were then amplified using PCR primers (page 443, col. 2)(limitations of Claim 3). As seen in Figure 1, GSTP hypermethylation of the promoter region, -408 to +197 was amplified in the describe method and then further amplified by primers directed to –220 to -57, but GSTP1 hypomethylation in the same region did not yield a PCR product, i.e., the amplification is selective that it only amplifies the target region if the site at which abnormal cytosine methylation occurs is methylated (Claim 1 (ii), 18-25, 35-39). The PCR amplification products are then electrophoresed on polyacrylamide gels and visualized by staining with ethidium

bromide or Southern blot hybridization analysis (page 444, col. 1)(limitations of Claim 1 (iii)). Lee teaches that using the PCR assay strategy, more than 90% of human prostatic carcinoma DNA specimens analyzed exhibited deoxycytidine methylation changes extensively encompassing the GSTP1 promoter region (page 443, col. 2).

Lee suggests that bisulfite detection may prove useful as molecular staging and diagnosis strategies (page 449, col. 1). Moreover, Lee teaches that methylated CG dinucleotides can be distinguished from CG dinucleotides at specific genomic DNA loci by several means potentially amenable to use with DNA amplification strategies including treating amplified DNA with bisulfite to promote selective deamination of C nucleotides to U nucleotides that permits discrimination of C nucleotides from methylated C nucleotides as differences in the nucleotide sequence of the amplification product accompanying bisulfite treatment (page 446, col. 1). Lee does not specifically teach the benefit of using bisulfite treatment for distinguishing methylated DNA from unmethylated DNA.

However Herman et al. (herein referred to as Herman) teaches methylation specific PCR (MSP) for rapid identification of DNA methylation patters in a CpG containing nucleic acid (abstract). Herman reviews numerous ways that methylation had been previously detected, including methylation-sensitive enzymes, Southern hybridization with methylation sensitive restriction enzymes and methylation sensitive enzymes and the PCR (col. 2-3). Herman teaches that each of these methods have drawbacks which makes utizilizing bisulfite treatment of DNA to convert all unmethylated cytosines to uracil followed by PCR advantageous. Herman teaches a

method for rapid assessment of the methylation status of any group of CpG sites within a CpG island independent of the use of methylation-sensitive restriction enzymes (col. 3, lines 40-45). Herman teaches that with MSP, all CpG sites, not just those within sequences recognized by methylation-sensitive restriction enzymes may be analyzed (col. 5, lines 1-4). Further MSP also eliminates the frequent false positive results due to partial digestion of methylation-sensitive enzymes inherint in previous PCR methods for detecting methylation (col. 5, lines 5-10). MSP requires only small amounts of DNA, is sensitive to 0.1% of methylated alleles of a given CpG island locus, and can be performed on DNA extracted from paraffin-embedded samples (col. 3, lines 50-55). MSP eliminates the false positive results inherent to previous PCR-based approaches which relied on differential restriction enzyme cleavage to distinguish methylated from unmethylated DNA (col. 3, lines 55-58). Herman teaches that MSP primers are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified by the invention assay (col. 4, lines 55-60). Herman compares MSP to the only technique that can provide more direct analysis, namely genomic sequencing. MSP is much simpler and requires less time than genomic sequencing, avoids the use of expensive sequencing reagents and the use of radioactivity, and increased sensitivity (col. 5, liens 15-30). The MSP method comprises contacting a methylated CpG containing nucleic acid specimen with an agent that modifies unmethylated cytosine, amplifying the CpG containing nucleic acid in the specimen by means of CpG-specific oligonucleotide primers and detecting the methylated nucleic acid (col. 5, lines 40-47). Herman teaches that the preferred agent

for modifying unmethyalted cytosine is sodium bisulfite (limitations of Claim 2, 8, 40-41). Herman teaches that cytosine reacts with the bisulfite ion to form a sulfonated cytosine reaction intermediate which is susceptible to deamination, giving rise to a sulfonated uracil (col. 5, lines 60-62). Uracil is recognized as a thymine by Taq polymerase and therefore upon PCR, the resultant product contains cytosine only at the position where 5-methylcytosine occurs in the starting template DNA (col. 5, lines 63-67)(limitations of Claim 4-5). Herman teaches that the method of amplifying is by PCR preferably (col. 8, lines 58-59)(limitations of Claim 9). Herman teaches that the primers specifically distinguish between untreated DNA, methylated and non-methylated DNA. MSP primers usually contain relatively few Cs or Gs in the sequence since the Cs will be absent in the sense primer and Gs absent in the antisense primer (col. 6, lines 5-10)(limitations of Claim 7, 10, 11, 13). The primers typically contain 12-20 or more nucleotides, although they may contain fewer nucleotides (col. 6, lines 34-37)(limitations of Claim 6, 12). Herman teaches that any specimen in purified or nonpurified form can be used. The specimen may be from any source including prostate, lung (col. 7, lines 30-35). The nucleic acid is in the region of the promoter of a structural gene typically (col. 10, lines 17-19). Herman teaches that the detection of the methylated CpG containing nucleic acid in the specimen may be indicative of cellular proliferative disorder or neoplasia including prostate cancer.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methylation detection method of Lee with the methylation detection method of Herman. The ordinary artisan would have realized based upon the

explicit teachings of Herman, that the method of using methylation specific primers was advantageous over digestion with methylation-sensitive enzymes followed by PCR. Herman specifically states, "MSP eliminates the false positive results inherent to previous PCR-based approaches which relied on differential restriction enzyme cleavage to distinguish methylated from unmethylated DNA". Herman also additional advantages of using MSP detection methods as compared to other methylation detection methods. MSP detection uses isolated DNA which is not treated with a methylation sensitive restriction endonuclease prior to amplification, which is exactly what is being claimed. Herman specifically points out the desirability of using MSP to avoid the use of enzymes. Since Herman has specifically compared the methylation detection method of Lee with the modified methylation detection method of Herman and found that the MSP methylation detection method has benefits, the ordinary artisan would have been motivated to have used the MPS methylation detection method. Therefore, the ordinary artisan would have been motivated to have modified the method of detecting methylation in the promoter region of Lee with the MSP methylation detection method of Herman for the explicit benefits taught by Herman.

Response to Arguments

The response traverses the rejection. The Declaration under 1.132 by Dr. Peter Molloy has been carefully considered.

The response asserts that the evidence presented in the Declaration demonstrates that Lee does not further add to the understanding of which CpG show differential methylation between cancer and normal tissue. This argument has been

thoroughly reviewed and considered, however the claims are not specifically drawn to particular CpG sites that are differentially methylated. The claims are broadly drawn to amplifying a very large region to determine whether amplification occurs as indication of cancer. The declaration (para 8) specifically states that Lee and Herman demonstrate that sites -34 and -35 are not detectably methylated in normal tissue but is significantly methylated in 20 of 20 cancer specimens studies. The declaration (para 8) further states that two further restriction enzyme sites (-17, -18, -13, -12) are methylated. Based upon the teachings of Lee and Herman, as specifically provided in the declaration, the claims clearly encompass these CpG sites which are differentially methylated. Since the ordinary artisan would understand they were differentially methylated, the ordinary artisan would have been motivated to have used the methylation specific amplification taught by Herman, for the reasons already of record. The declaration has provided a drawning believed to illustrate the state of the art prior to the disclosure which specifically provides particular CpG sites which are differentially methylated between cancer and normal tissue. Thus, given that this was know prior to the disclosure, the ordinary artisan would have been motivated to have used the method of Herman for methylation specific PCR.

The response asserts and the Declaration states that levels of methylation at individual CpG sites within promoter or CpG islands could vary substantially. This argument has been thoroughly reviewed and considered. The examiner appreciates this aspect of methylation. The art appears to support that the presence of one methylated site is not necessarily indicative of methylation at each of the other sites,

however, the claims are not particularly drawn to detecting methylation at any particular site.

The Declaration (para 16) states that while the ordinary artisan would be presented with the information in the art, the ordinary artisan's would lack the knowledge of which regions and specific CpG sites provide clear discrimination between cancer and normal tissue DNA. It is noted that the MPEP provides in 716.02(a) that "Presence of a property not possessed by the prior art is evidence of nonobviousness." Further the MPEP states in MPEP 716.02(d), "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." This argument has been thoroughly reviewed and considered, however, the claims are not specifically drawn to any particular regions or specific CpG sites which would provide clear discrimination between cancer and normal tissue DNA. As written the claims are drawn to require amplification of the entire target region, namely nucleotides 836-1117 of SEQ ID NO 60. This however does not appear to be commensurate in scope with the arguments directed to particular CpG sites or regions.

The Declaration (para 16) further asserts that "it could not be automatically assumed that the MSP method could be applied to any subset of the HpaII sites in order to provide an assay that discriminated cancer from normal DNA." Further, the

Declaration (para 19) states that "in order to predictably apply the MSP method without several amplification steps, the ordinary artisan would have had to be aware of the existence of the CpG sites that show consistent differences between cancer and normal tissue." This argument has been thoroughly reviewed and considered, however, the claims are not commensurate in scope with this assertion. The claims are not drawn to any particular sites, but are rather broadly drawn to amplifying a target region comprising nucleotides 836-117. Thus, the claims require amplification of nearly 300 nucleotides. This is not commensurate with the arguments requiring amplification of particular sites.

The response on page 22 asserts that Claim 77 is directed to CpG sites 1-55 of the GST-Pi gene and there is no teaching or suggestion in the references directed to this area. The Declaration (para 24) asserts that Herman teaches "differences did not extend within the gene and that intragenic sequences were methylated in both expressing and non-expressing cells." The examiner has reviewed Herman and Lee at great length and can not identify the citation provided by the declaration in para 24.

The response dated February 6, 2003 focuses on the ability of Lee to simultaneously detect all 12 recognition sequences for HpaII and MSP1 in a sample DNA. The response further poses the question of what the result would be for the modification of detecting methylation in the promoter region of Lee with the MSP method of Herman. The response points out, correctly, that the primers need to be in close proximity to the CpG sites. The ordinary artisan would have clearly recognized this aspect of the MSP method from the teachings of Herman. Moreover, the teachings

of Lee include methylation CpG sites over a large region. The ordinary artisan would have recognized that several different amplifications may need to be performed to analyze the complete region. Herman teaches examining regional aspects of CpG island methylation (col. 14). Herman also teaches that MSP allows examination of all CpG sites, not just those within sequences recognized by methyaltion sensitive enzymes; MSP eliminates the frequent results due to partial digestions. Moreover, Herman specifically compared the methylation detection method of Lee with the modified methylation detection method of Herman and found that the MSP methylation detection method has benefits, the ordinary artisan would have been motivated to have used the MPS methylation detection method. The suggested "primer" of several hundred nucleotides in length is not how Herman solves the problem of multiple CpG sites. The primers of Herman "preferably have a T in the 3' CG pair to distinguish it form the C retained in the methylated DNA." Therefore, it is clear from Herman that various primer pairs are used to distinguish between methylated or unmethylated, i.e. abnormal methylation. A single primer is not used to distinguish all recognition sites in a promoter region as suggested by the response.

The response dated February 6, 2003 asserts that the ordinary artisan would "not have seen the relevance of Herman's MSP method based on oligonucleotide primers to the detection of the extensive methylation marker taught by Lee et al." (page 19 of response). This argument has been thoroughly reviewed, but is not found persuasive because Herman teaches using multiple primer pairs for different methylation sites. Moreover, Lee strongly suggests that using bisulfite treated DNA can discriminate

between C nucleotides and methylated C nucleotides as differences in amplification. Therefore, given the expected benefits taught by Herman for using MSP, the ordinary artisan would have been motivated and expected use the improved MSP method over the digestion methods.

Lee teaches that the CpG sites within the region of the GST-Pi gene and/or its regulatory flanking region can be used as a marker for prostate cancer. Thus for the reasons above and those already of record, the rejection is maintained.

11. Claims 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June 1997) in view of Herman et al. (US Pat. 5,786,146, July 1998) as applied to Claims -14, 17-25 and newly added claims 75-91, above and further in view of Jhaveri (Gene, Vol. 210, pages 1-7, March 1998) and Morrow et al (Genbank Accession Number M24485, December 1994).

Neither Lee nor Herman teach the specific primers for the amplification of the CpG island of GST-Pi.

However, Jhaveri et al. (herein referred to as Jhaveri) teaches the regions of GST-Pi which are methylated. Jhaveri teaches that the CpG island spans the proximal promoter and the first and second exon and intron.

Morrow teaches the full GST-Pi sequence which includes the proximal promoter, the first and second exon and intron.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the primers taught by Lee to obtain additional primers for amplification of the CpG island. The ordinary artisan would have recognized based upon the teachings of Jhaveri that one would desire amplifying the proximal promoter, first and second exon and intron. Given the full GST-Pi sequence, the ordinary artisan would have been able to have generated primers which flank these sequences or are directed to specific subsequences within the CpG island for amplification and analysis of the CpG island which allows diagnosis of prostate cancers. Therefore, the instantly claimed primer pairs are functional equivalents to the primer pairs taught by Lee in view of Herman. Herman teaches the general design of MSP primers. Namely, Herman teaches MSP primers usually contain relatively few Cs or Gs in the sequence since the Cs will be absent in the sense primer and Gs absent in the antisense primer (col. 6, lines 5-10). The primers typically contain 12-20 or more nucleotides, although they may contain fewer nucleotides (col. 6, lines 34-37). Therefore, taking the primers taught by Lee in view of Herman and obtaining alternative functional equivalents which may also amplify the CpG island regions of interest, taught by Jhaveri, would have been well within the guidance provided in the art for the ordinary artisan. The art provides a specific region to design primers to for the detection of methylation, provides how to generate primers which will differentiate methylated nucleic acids from unmethylated nucleic acids and provides a clear advantage of using MSP primers for the differential methylation detection. Therefore, the instant primers of SEQ ID NO: 1-16 are merely functional equivalents for those already taught in the art. Since the claimed

oligonucleotides simply represent functional equivalents concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations.

Response to Arguments

The response traverses the rejection. The response asserts that Jhaveri and Morrow do not provide the deficiencies from Lee and Herman. This argument has been reviewed but is not convincing for the reasons discussed above. Jhaveri and Morrow are used to illustrate primers may be used within these regions and provide the sequence therefore. The Declaration (para 27) provides that Figure 4A, Panel A illustrates that not all MSP primer sets designed to the GSTP1 sequences provide sufficient discrimination between cancer and normal DNA. This argument has been thoroughly reviewed and considered. The instant specification and arguments are unclear which primer pairs and sequences were illustrated in each of these Figures. Absent the secondary considerations, which have not been filed herein, the unexpected results of primers has not been established. Thus for the reasons above and those already of record, the rejection is maintained.

12. Claims 30-34, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (Cancer Epidemiology, Biomarkers, Prevention. Vol. 6, pages 443/450, June 1997) in view of Herman et al. (US Pat. 5,786,146, July 1998) as applied to Claims 1-25, above and further in view Tchou et al (Hepatology, Vol. 28, No. 4, pages 47, October 1998).

Lee in view of Herman does not specifically teach detecting hypermethylation in GST-Pi as an indicator of liver cancer (hepatocellular carcinoma).

However, Tchou et al. (herein referred to as Tchou) teaches the role of GST-Pi expression in hepatocarcinogenesis. Given the teachings that GST-Pi is hypermethylated in prostate cancer, Tchou hypothesized the same phenomenon may occur in HCC. Tchou teaches that CpG methylation is a common phenomenon in HCC. Using PCR-based methylation assay, none of the normal tissues have evidence of CpG methylation near the promoter, however, 18 of 20 tumors showed methylation in that region.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the teachings of Lee in view of Herman for detecting prostate cancer based upon differential methylation of GST-Pi with the teachings of Tchou that GST-Pi is also hypermethylated in hepatocellular carcinoma. Therefore, the ordinary artisan would have been motivated to have applied the PCR-based methylation method for screening for liver cancer using the same assay as taught in the art for prostate cancer. The ordinary artisan would have been able to have taken samples from the two organs and performed analysis on each of the samples to obtain a more comprehensive analysis of the patients cancer status.

Response to Arguments

The response traverses the rejection. The response asserts that Tchou does not provide the deficiencies from Lee and Herman. This argument has been reviewed but is not convincing for the reasons discussed above. The response further asserts that

Tchou is published after the priority document. This argument has been thoroughly reviewed, but is not found persuasive the priority document fails to provide enabling disclosure for the association of any methylation with liver cancer. The passage on page 22 of the priority document does not particularly draw any association between cancer and methylation. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

13. No claims allowable.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
April 18, 2005